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Transesophageal Echocardiographic Monitoring of Preoperative Acute Hypervolemic Hemodilution

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Background: **Preoperative acute hypervolemic hemodilution is used in anesthesia to reduce the loss of blood cells during intraoperative bleeding. Indications for use of the technique might be broadened if it can be shown to be safe in older as well as younger patients. Few data are available describing heart function in humans subjected to hypervolemic hemodilution.**

Methods: **Nineteen anesthetized Jehovah's Witnesses (ages 22–70 yr) without evidence of heart disease had hypervolemic hemodilution before surgery in three stages, each consisting of an infusion of 500 ml dextran 40 (50 g/l) and 500 ml Ringer's lactate over a 10-min period. After each stage, the size and function of the left ventricle were recorded by transesophageal cross-sectional echocardiography in the short-axis view. Simultaneously heart rate, arterial blood pressure, pulmonary arterial and wedge pressures and cardiac output were recorded, to compare the echocardiographic and hemodynamic data.**

Results: **No complications occurred. Hypervolemic hemodilution resulted in an increased cardiac output by increasing the stroke volume from 48 ml in basal conditions to 67, 71, and 72 ml over the three stages, whereas heart rate did not increase. There was an initial increase in end-diastolic volume of the left ventricle, as assessed from the cross-sectional end-diastolic area from 12.9 to 15.5, 16.6, and 16.9 cm^2 followed by a decrease in the in cross-sectional end-systolic area from 6.3 to 6.8, 6.0, and 5.7 cm^2. The increase in wedge pressures (from 5.9 to 12.4, 17.9, and 22.6 mmHg) did not lead to progressive cardiac dilation. There was a curvilinear relation between wedge pressure and cross-sectional end-diastolic area. Stroke volume did not decrease, nor did cross-sectional end-systolic area increase; instead, a decrease in end-systolic area was a common observation.**

Conclusions: **The described regimen of acute hypervolemic hemodilution is well tolerated during anesthesia by patients without heart disease and does not lead to cardiac failure. It leads to an increase in stroke volume that is generated initially from an increase in end-diastolic volume, followed in many patients by a decrease in end-systolic volume, the mechanism of which is as yet unclear. (Key words: Blood: transfusion. Measurement techniques: transesophageal echocardiography. Transfusion, hemodilution: hypervolemic.)**

PREOPERATIVE acute hypervolemic hemodilution is used to reduce the loss of blood cells during intraoperative bleeding and thus avoid the need for blood transfusion. After surgery the hematocrit is partially restored by administering diuretics to remove the excess of intravascular fluid. To date, hypervolemic hemodilution usually has been used in patients who need major surgery but refuse (often for religious reasons) all blood transfusion, including autologous. The indications, however, could be expanded to include any major surgery if the potential risks (especially the risks of acute cardiac failure and pulmonary congestion) can be proven to be low. Our initial experience showed that the procedure is clinically safe.[1,2]

In this study we describe in greater detail the effects of acute hypervolemic hemodilution on cardiac size and function and the relation of this echocardiographic information to hemodynamic information obtained through pulmonary artery catheterization and systemic pressure monitoring.

Materials and Methods

Nineteen patients (3 men and 16 women) undergoing preoperative acute hypervolemic hemodilution were studied. Their ages were 22–70 yr (mean 48 yr) and

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their weights 48–99 kg (mean 70 kg). All patients were Jehovah's Witnesses who refused any blood transfusion. All had to undergo procedures with an expected significant blood loss. Four were scheduled for orthopedic surgery, the remainder for oncologic surgery. All were informed in detail on the procedure and gave written informed consent before surgery. The study protocol was approved by the Medical Ethical Committee of the University Hospital Rotterdam-Dijkzigt.

Any evidence of heart disease was an exclusion criterion for hypervolemic hemodilution. Eligible patients were referred to our hospital after screening for heart disease. None of the referred patients was subsequently excluded. One patient had a history of mild hypertension, and one had a history of hypertension and chest discomfort without documented ischemia. The others had no evidence of cardiovascular disease in the history or physical examination or on the preoperative electrocardiogram or chest x-ray.

After receiving 2.5 mg midazolam orally, two venous cannulae, an arterial cannula (radial artery), and a pulmonary artery thermodilution catheter (Swan-Ganz, American Edwards Laboratories) were inserted and calibrated to room air for the zero-level of the pressure. Heart rate, arterial blood pressure, right atrial pressure and pulmonary artery pressure were recorded continuously (Horizon, Mennen Medical). The pulmonary capillary wedge pressure (PCWP) was measured intermittently, as a mean pulmonary occlusion pressure at end-expiration. Cardiac output was determined by thermodilution as a mean of three consecutive measurements. A five-lead electrocardiogram (leads X, Y, Z, V2, and V5) was monitored continuously in combination with automated ST-segment analysis. Standard 12-lead electrocardiograms were obtained in all patients 1 day preoperatively, 1 day postoperatively, and 5–8 days postoperatively.

Anesthesia were induced with fentanyl 5 μg/kg, thiopental 5 mg/kg, and pancuronium 0.1 mg/kg. After tracheal intubation the lungs were ventilated with 70% nitrous oxide in oxygen, and tidal volume was adjusted to achieve normocapnia. Anesthesia was maintained with enflurane (end-tidal 0.4 vol%). No additional fentanyl was administered during the hypervolemic hemodilution. After induction of anesthesia a transesophageal ultrasound probe (5-MHz transducer connected to a Toshiba SSH 160 ultrasound machine) was introduced for continuous and real-time imaging of the heart. The transducer was positioned in the stomach to obtain a two-dimensional short-axis view of the left ventricle at the level of the papillary muscles. After the optimum view had been obtained, the steering mechanisms of the probe were locked and the probe was carefully secured to maintain the identical cross-sectional view throughout the preoperative hypervolemic hemodilution.

After a stabilization period of 15 min after induction of anesthesia, baseline hemodynamic data were recorded; blood gas samples were drawn from the arterial and pulmonary arterial catheters; and for 1 min the echocardiographic short-axis view of the left ventricle was recorded on videotape for subsequent analysis.

Hypervolemic hemodilution was then undertaken in three equal stages. Each stage consisted of the infusion of 500 ml dextran 40 (50 g/l) and 500 ml Ringer's lactate over a 10-min period. After each stage, all measurements and a recording of the echocardiogram were repeated. The whole procedure took 45–50 min in all patients. Surgery did not start until the hypervolemic hemodilution and all the measurements had been completed.

The echocardiographic two-dimensional images were analyzed off-line from the videotape recordings. Adequate echocardiographic recordings were available for 17 of 19 patients; for 1, the images were lost after a technical error, and for another the image quality was inadequate for analysis. Of three consecutive cardiac cycles, the end-diastolic and the end-systolic echoframes were selected. The end-systolic frame was defined as the one with the smallest enclosed area of the left ventricular cavity. (In case of doubt, several were measured to find the smallest.) The end-diastolic frame was defined as the one with the largest enclosed area, and this always happened to be the first frame on which the QRS complex was visible on the synchronously recorded electrocardiogram. The endocardial borders of the left ventricle were traced with a hand-held input device (a "mouse") and a digitizing tablet connected to a microcomputer-based analysis system, used to calculate the enclosed area of the left ventricular cavity. Data of three cardiac cycles were averaged, and if two measurements differed by more than 10% the data were rejected and the tracing was repeated using three other cardiac cycles.

Analysis of variance with subsequent t tests were used for all hemodynamic and echocardiographic variables to identify any significant changes during hypervolemic hemodilution and to determine the stages between which the changes were significant. Level of significance was defined as $P < 0.05$.

Results

Preoperative acute hypervolemic hemodilution was completed in all patients according to the protocol without complications, and all patients subsequently underwent uneventful surgery without blood transfusions. The mean values for the whole group are summarized in table 1.

Hypervolemic hemodilution resulted in an increase in cardiac output by 36%, solely the result of an increase in stroke volume because heart rate, after an initial decrease, was unchanged. This was a consistent finding in all individuals (figs. 1 and 2).

The cross-sectional end-diastolic area (EDA) initially increased in all patients. However, in most patients the EDA reached a maximum at some point in time during the volume loading, beyond which there was no further increase in EDA despite a further increase in PCWP. The relation between EDA and PCWP was curvilinear for the mean values (table 1) as well as for most individual patients (fig. 3). There was a wide range in the volume of fluid infused before the maximum EDA was reached; in 5 of 17 patients the EDA did not increase after the first liter, in 5 of 17 the maximal EDA was reached after 2 liters infusion and in 7 of 17 patients the largest EDA was present after infusion of 3 liters. In these 7 patients, however, increases from the previous recording were minimal. The maximal EDA was usually reached at PCWPs between 15 and 18 mmHg.

The change in cross-sectional end-systolic area (ESA) was variable. In 12 of 17 patients a decrease in ESA was observed, which had commenced at the stage when EDA had reached its maximum in 10 of these 12, whereas in two patients the ESA had started to decrease one stage earlier. In 5 patients no decrease in ESA was observed, and 4 of these were patients in whom the EDA was still increasing at the final stage of the study. Because there was considerable variation among patients in the amount of fluid infused before a decrease in ESA, the mean changes in ESA (table 1) are somewhat blunted with a significant decrease only between the second and third stages of hemodilution.

Hypervolemic hemodilution was associated with a steep increase in PCWP (table 1 and fig. 3). Although the PCWP correlated closely with the amount of fluid infused in the individual patient, the amount of fluid required to reach a certain level of PCWP varied widely among patients, depending also on the PCWP at baseline. In 4 of 19 patients PCWP had exceeded 15 mmHg

Table 1. Hemodynamic Data

Volume Load (ml)	Hct (%)	CO (L/min)	HR (beats/min)	BP_{sys} (mmHg)	BP_{dias} (mmHg)	BP_{mean} (mmHg)	PCWP (mmHg)	SV (ml)	LVSW (g/min)	SVR (dyne·s·cm^5)	EDA (cm^2)	ESA (cm^2)	SF (%)	σES
Baseline	37 (3)	4.4 (1.1)	93 (14)	105 (21)	66 (10)	81 (14)	5.9 (2.6)	48 (11)	49 (14)	1,498 (626)	12.9 (3.5)	6.3 (2.6)	6.7 (6.5)	148 (58)
1,000	32 (3)*	5.5 (1.3)*	83 (15)*	114 (20)*	67 (10)	87 (14)*	12.4 (3.0)*	66 (15)*	67 (19)*	1,197 (461)*	15.5 (3.3)*	6.8 (2.6)	6.8 (6.4)	162 (61)
2,000	29 (3)*	5.8 (1.5)*	82 (14)	117 (23)	68 (11)	88 (15)	17.9 (3.8)*	71 (17)*	68 (24)	1,063 (391)*	16.6 (3.4)*	6.0 (2.3)*	7.1 (7.7)	163 (55)
3,000	26 (3)*	6.0 (1.5)	83 (14)	121 (21)	70 (11)	92 (14)	22.6 (4.2)*	72 (18)	68 (23)	1,012 (307)	16.9 (3.7)	5.7 (2.1)	8.0 (8.6)	162 (47)

Values are mean (SD).

Hct = hematocrit; HR = heart rate; SV = stroke volume, BP_{sys} = systolic arterial blood pressure; BP_{dia} = diastolic arterial blood pressure; BP_{mean} = mean diastolic blood pressure; PCWP = pulmonary capillary wedge pressure; LVSW = left ventricular stroke work; SVR = systemic vascular resistance; EDA = end-diastolic cross-sectional area of the left ventricular cavity; ESA = end-systolic area; SF = pulmonary shunting fraction; σES = end-systolic wall stress.

* $P < 0.05$ *versus* the previous measurement.

Table 2. Distribution of Sex, Age, and Weight of the 19 Patients

Patient No.	Sex	Age (yr)	Weight (kg)
1	F	43	48
2	F	50	74
3	F	44	61
4	F	42	55
5	F	48	68
6	F	59	64
7	M	22	65
8	F	68	64
9	M	70	70
10	F	49	88
11	M	44	99
12	F	49	90
13	F	41	57
14	F	50	69
15	F	49	70
16	F	54	88
17	F	46	86
18	F	51	55
19	F	38	66

already after infusion of 1,000 ml, in 10 of 19 patients after the infusion of 2,000 ml, in 3 patients after 3,000 ml, whereas in 2 patients PCWP was still less than 15 mmHg after the infusion of 3,000 ml fluid.

In four of the five patients with the greatest increase in PCWP (ending at 25, 28, 26, 26, and 30 mmHg)

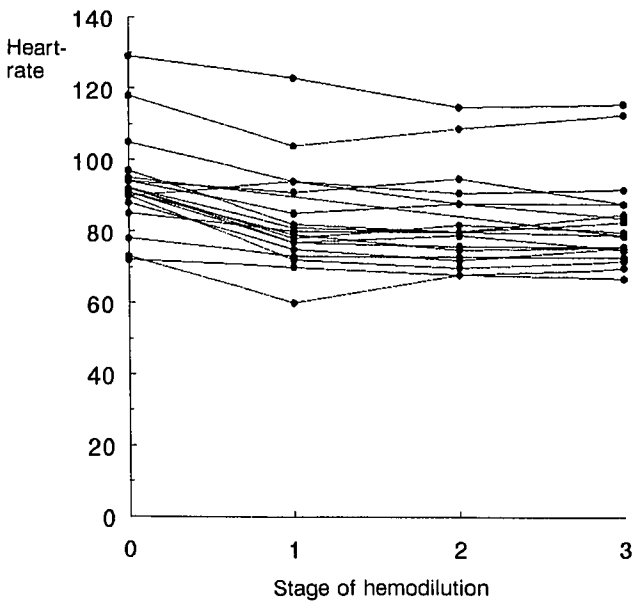

Fig. 1. Heart rate of individual patients during hypervolemic hemodilution.

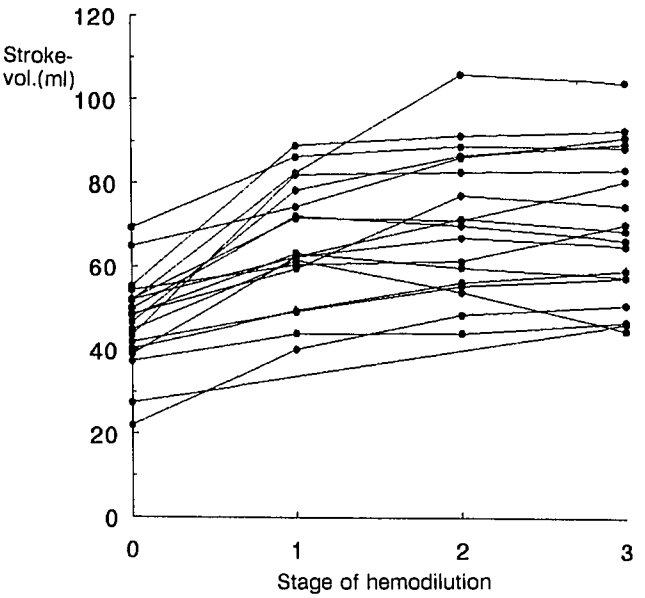

Fig. 2. Stroke volume of individual patients during hypervolemic hemodilution.

EDA had reached its maximum after infusion of 1,000 ml (at PCWPs of 14, 16, 14, and 16 mmHg) and had not increased thereafter.

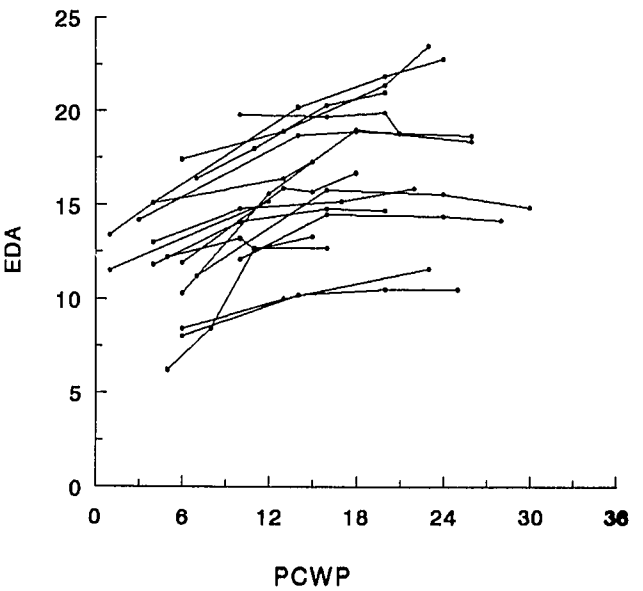

Fig. 3. Changes in echocardiographic end-diastolic area (EDA) during hypervolemic hemodilution in individual patients *versus* simultaneously measured pulmonary capillary wedge pressure (PCWP).

In one patient in this series, there was a decrease in cardiac output before the completion of hemodilution (from 5.9 to 5.1 l/min during the final stage) associated with an increase in ESA (from 6.2 to 7.0 cm^2), suggesting that cardiac function was depressed. However, these changes were associated with a significant increase in systemic vascular resistance (SVR) and mean arterial blood pressure (from 79 to 101 mmHg) and not by any sign of ischemia. In all other patients, the cardiac output was either increasing or stable throughout hypervolemic hemodilution.

No regional wall motion abnormalities of the left ventricle, indicating myocardial ischemia,[3] were encountered. In one patient, aged 70 yr, ST-segment changes of just less than 0.1 mV developed after induction of anesthesia, resolved during the initial stages of hemodilution, and than returned at maximal infusion. There were no other patients with intraoperative ST-segment changes, nor were the postoperative electrocardiograms different from the preoperative electrocardiogram in any patient.

No pulmonary or ventilatory problems were encountered despite the high PCWPs. No positive end-expiratory pressure ventilation was used in any patient. At an unchanged inspired oxygen fraction of 30% and with tidal volumes adjusted to maintain normocapnia, the systemic arterial and mixed venous oxygen tensions remained unchanged, in accordance with our previously reported experience.[2] Pulmonary shunt fractions were stable for each individual patient and at group level (table 1), despite considerable variation among patients.

Discussion

Hypervolemic hemodilution caused an increase in cardiac output resulting entirely from an increase in stroke volume; heart rate and arterial blood pressure remained unchanged. This observation is in agreement with other studies in which acute hypervolemic hemodilution was used in humans.[4–7]

Initially the increase in stroke volume was generated from an increase in the end-diastolic volume of the left ventricle, suggesting a Frank-Starling effect, up to a maximum, which was reached at PCWP of approximately 15–18 mmHg. With further filling there was only an insignificant increase in the end-diastolic volume, even when PCWPs of as much as 28 or 30 mmHg were achieved. This is in agreement with previous animal experiments.[8] It is well known that healthy myocardium has an extremely low distensibility when sarcomere length exceeds 2.2 μm, and it is almost impossible to stretch a strip of cardiac muscle to sarcomere lengths greater than 2.4 μm. This has been explained by the presence of a collagen skeleton that surrounds the cardiac muscle fibers and that constitutes an effective protection against acute dilatation. Also the pericardium has a role in limiting acute cardiac dilatation. More insight into the relative importance of these mechanisms might be obtained from simultaneous measurements of intrapericardial pressure. No clinical experience is available on hypervolemic hemodilution in patients who have had a previous pericardiectomy. Some animal studies suggest that the left ventricle does not need the pericardium as a protective mechanism against acute dilatation, in contrast to the right ventricle.[9] Few data are available in humans. Mangano *et al.*[10] showed that the muscle of the left ventricle itself, and not the pericardium is the major determinant of diastolic compliance when filling pressures and volumes are moderately increased. However, others do attribute a role to the pericardium in protecting the left ventricle from progressive dilatation in acute increases in volume load in the range our patients received.[11] The clinical implication is that it might be dangerous to apply hypervolemic hemodilution in patients who have undergone a previous pericardiectomy.

The end-systolic volume of the left ventricle decreased with further hypervolemic hemodilution. This change could be due to a decrease in afterload, a Frank-Starling effect, an increase in myocardial inotropic state, or some combination of these effects. Studies in animals undergoing normovolemic hemodilution have shown that a decrease in hematocrit leads to an increased stroke volume that is generated from both a (slight) increase in end-diastolic volume (despite normovolemia in these experiments) and a decrease in end-systolic volume.[12] This decrease in end-systolic volume was then attributed to a decrease in afterload due to the lowered blood viscosity. The identical decrease in end-systolic volume was seen when animals were prevented from increasing their inotropic state by β-adrenergic blockade. In our patients, however, no decrease in arterial pressure was encountered because the decrease in SVR was compensated by the larger stroke volume, resulting in minor changes in systemic arterial pressures. A simplified estimate of end-systolic

wall stress, as an index of afterload, remained unchanged (table 1).#

A possible explanation is that after maximal EDA is achieved, a state of stable optimal performance exists in which ESA is dependent mainly on SVR. When we review the correlation between ESA and SVR in our patients after maximal EDA was achieved, the limited number of data do suggest such a direct correlation (fig. 4).

Our results are different from those of a study in humans by Mangano *et al.*,[13] who reported an increase in end-systolic volume and a decrease in ejection fraction when increasing the preload. There are, however, several differences in study design that may explain these opposite findings. First, they infused 1,500 ml whole blood rather than plasma-expanders. Their decrease in SVR was small compared to ours, and arterial blood pressure increased considerably. Second, they studied patients immediately after coronary bypass surgery, and 13 of 15 patients had one or more previous myocardial infarctions. Hearts damaged by ischemic heart disease might respond differently to volume loading. Third, because PCWP in their study increased from 2 to 7 mmHg, their patients shifted from hypovolemia to normovolemia. The tendency to decrease end-systolic volume in our patients was observed only during hypervolemia. Indeed in our patients as well, the initial change in ESA often was an increase, especially in those who had a PCWP < 7 mmHg at baseline.

The decrease in SVR in this series cannot be explained by rheologic changes alone. Because of the nonlinear relation between hematocrit and blood viscosity,** the decrease in hematocrit from 37% to 25% would result in decrease in viscosity by 19%,

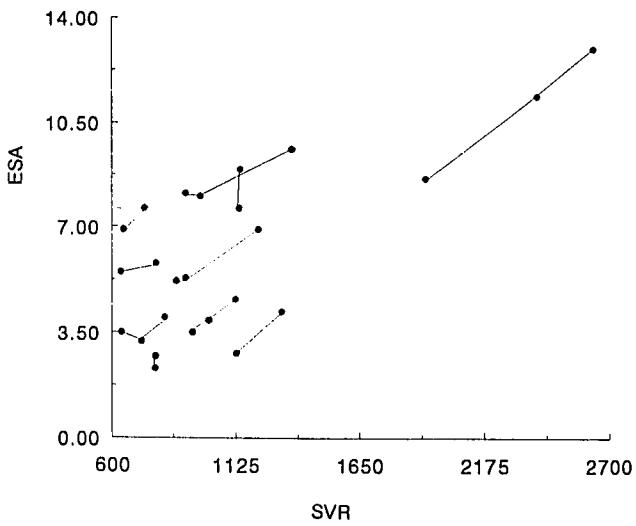

Fig. 4. Changes in echocardiographic end-systolic area after the maximal end-diagnostic area had been reached *versus* systemic vascular resistance.

presuming that the infused fluid has the same viscosity as plasma. Base on the viscosity of dextran 40 and Ringer's, this assumption is valid within a reasonable margin of error. Others have measured viscosity during hemodilution with combined Dextran 40 and crystalloids and could not demonstrate a change in plasma viscosity. But even if dilution had been performed with water, the predicted decrease in blood viscosity would be less than 30%. Because SVR decreased by 33% and because viscosity has a linear relation with SVR (Hagen-Poiseuille law), a net vasodilation must have occurred during hemodilution. This may be the result of the sum of the autoregulatory organ redistributions of circulating volume that occur in hemodilution.[14,15] Vasodilation may also have been caused by atrial natriuretic factor, the concentration of which rises steeply with acute hypervolemic hemodilution.[16] Other mechanisms that might in theory have decreased arteriolar tone include local tissue hypoxia, lactic acidosis or vasodilating metabolites such as adenosine. Unfortunately no measurements of atrial natriuretic factor, catecholamines or other neurohumoral factors were included in the study protocol. Another explanation might be the activation of vagal or nonmedullated receptors in the left ventricle, responding to ventricular distension and causing reflex arteriolar vasodilation.[17] This might also explain why the decrease in ESA started usually only after a maximal

The end-systolic wall stress (table 1) was calculated using a simplification of Laplace's law:

$$\text{stress } \sigma = P \times \frac{r}{2h},$$

where P = pressure; r = radius; and h = wall thickness. r was calculated from the area, making the assumption that the short-axis of the left ventricle is a circle. Wall thickness was not considered because changes in end-systolic wall thickness throughout hemodilution were within the margin of error of M-mode echocardiographic measurements.

** Predicted changes in blood viscosity (see discussion) are based on the empirical vand equation: $v = v_p(1 + 0.025\ H + 0.000735\ H^2)$, where v = blood viscosity; v_p = viscosity of plasma; and H = hematocrit (percentage).

EDA had been reached, rather than running parallel with hemodilution.

This study did not include patients with a history of ischemic heart disease, and it is unknown whether hypervolemic hemodilution can be performed safely in such patients. In animal experiments, coronary blood flow increased out of proportion to the increased cardiac output during hemodilution, and this was due not only to rheologic changes but also to autoregulatory coronary vasodilation.[14,18,19] It is not known to what extent vasodilation occurs in atherosclerotic coronary arteries. A lower viscosity may improve flow across a stenosis, but in addition steal effects may occur after coronary vasodilation.

As an alternative to hypervolemic hemodilution, isovolemic hemodilution has been used in patients who accept the reinfusion of their own blood during or after surgery. It is not known, from the current literature, whether the apparently more physiologic condition of normovolemia is beneficial to the hemodiluted patient. Withdrawal of blood results in a decrease in maximum oxygen transport capacity, which is unaffected in hypervolemic hemodilution. When hypervolemic hemodilution was compared to normovolemic hemodilution, the former was shown to result in a higher oxygen transport, peripheral oxygen delivery and aerobic exercise capacity.[20,21] In an animal study, Messmer *et al.*[22] demonstrated that acute hemodilution to a hematocrit of 0.07 was survived by all animals if they were kept normovolemic, but by none that was hypovolemic, thus stressing the importance of volume status for the compensatory mechanisms for acute hemodilution.

In conclusion, preoperative acute hypervolemic hemodilution was well tolerated in patients without evidence of heart disease. No adverse cardiac events were encountered. At unchanged heart rates, the stroke volume increased significantly. This increase was the result of both an increase in end-diastolic volume, as was to be expected on the basis of the Frank-Starling mechanism, and of a decrease in end-systolic volume. The mechanism of these changes is partially explained by the Frank-Starling effect and the decreased blood viscosity, but additional factors cannot be excluded. Further studies are required on the neurohumoral changes, the rheologic and arteriolar changes, the consequences of coronary artery stenosis and the effects of inotropic and β-blocker drugs in hypervolemic hemodilution.

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